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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

WILLIAM W JONES
6 JUNIPER LANE
MADISON CT 06443

EYLER, Y

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/976,886	Applicant(s) Rimm et al.
	Examiner Yvonne Eyler	Group Art Unit 1642

Responsive to communication(s) filed on Apr 12, 1999

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 1-14 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1-14 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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Response to Amendment

Claims 1-14 are pending and under consideration in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

1. The rejection of Claims 1, 2, 5, 6, 9, 10, 13 and 14 under 35 U.S.C. 102(e) as being anticipated by Levine et al. (U.S. # 5,834,217) OR under 35 U.S.C. 102(a and e) as being anticipated by Levine et al. (U.S. # 5,635,362) is withdrawn.
2. The rejection of Claims 1, 2, 5, 6, 9, 10, 13, 14 under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter is withdrawn.
3. The rejection of Claims 1-10, 13 and 14 under 35 U.S.C. 103(a) as being unpatentable over Levine et al. (U.S. # 5,834,217) or Levine et al. (U.S. # 5,635,362) as applied to claims 1, 2, 5, 6, 9, 10, 13, and 14 above and in view of Nagy (J Exfoliative Cytology, 123-133, 1965-IDS) is withdrawn.
4. The rejection of Claims 11 and 12 under 35 U.S.C. 103(a) as being unpatentable over Levine et al. (U.S. # 5,834,217) or Levine et al. (U.S. # 5,635,362) as applied to claims 1, 2, 5, 6, 9, 10, 13, and 14 above and in view of Wardlaw (U.S. # 4,156,570) is withdrawn.
5. The rejection of Claims 1, 2, 5, 6, 9, 10, 13, and 14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 5,834,217 is withdrawn.

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6. The rejection of Claims 3, 4, 7, and 8 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 5,834,217 as applied to claims 1, 2, 5, 6, 9, 10, 13, and 14 above in view of Nagy (J Exfoliative Cytology, 123-133, 1965-IDS) is withdrawn.

Claim Rejections Maintained:

7. The rejection of Claims 1-14 under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Applicant argues that the rejection does not meet USPTO requirements because of the combination of 112 first and second paragraph rejection, which is averred to be scrambled. Applicant further argues that the claims have not been read in light of the specification and the level of one of skill in the art. Applicant concludes that if the level of skill of a cytologist and the teachings of the specification were considered, then rejection of the claims would be silly.

These arguments have been considered but are not found to be persuasive.

The rejections under 112 first and second paragraphs were combined for efficiency and such combination does not fall short of USPTO requirements, with the language used being a standard form paragraph. One of skill (to be addressed later) cannot be enabled to practice the invention if one of skill cannot determine what the invention encompasses. Thus, the two rejections, which were interrelated for this reason, were combined. At applicants request, the

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separate issues under both 112 second and first paragraph will be summarized, with claim numbers for each instance of the language. Applicant also indicated that the use of the word "confusing" was not clear. The word "confusing" was used as a substitute for the words "vague and indefinite." Applicant has requested clarification of why the language is confusing (i.e. vague and indefinite) which will be summarized below as well.

Summary of rejections under 112 second paragraph (found on pages 2-8 of the Office

Action of 3/31/99):

- "abnormal" cells, found in claims 1, 2, 8, 9, (dependent claims 10, 11, 12), and 13. The metes and bounds of what cells are encompassed and included as abnormal cannot be determined. What specific characteristics render a cell abnormal?

- "well-defined zone" or "well-defined annular zone," found in claims 1, 2, 3, 4, 5, 6, 7, 8, 9, (dependent claim 10), 11, (dependent claim 12), 13, and 14. The metes and bounds cannot be determined. There are no identifying characteristics of the zone supplied so that one of skill knows the properties that facilitate identification of the zone. The recitation that the zone is formed by various embodiments of an insert does not clarify the language.

- "epitopic-specific labeling agents", "epitopic labeling materials", "epitopic-specific which highlight", or "epitopic-specific agents which signal" found in claims 1 (line 5), 2(lines 4-6), 3(line 4), 4(lines 4-5), 5(lines 3-5), 6(lines 4-6), 7(lines 4-5), 9(lines 6-7), (dependent claims 10-12), 13(lines 7-8), 14(lines 4-6). The metes and bounds of the agents and materials cannot be determined. Identifiable, measurable, definitive characteristics of the agents are not provided, nor are targets which the agents bind defined thus one cannot determine or identify the compounds encompassed.

- "stains or colorants that clarify cell morphology" or "cell morphology clarifying stains" found in claims 1.(lines 8-9), 2 (lines 6-7), 3 (lines 5-6), 6 (lines 6-7), 8 (lines 4-5), 9 (lines 8-9), (dependent claims 10-12), 13 (lines 9-10), 14 (lines 8-9). Are vague and indefinite because it is not clear what the identifying characteristics of the stains and colorants are. The metes and bounds of the compounds encompassed cannot be determined. This was combined with the following rejection regarding clarified or abnormal morphology which speaks to the function of the compounds, which cannot be identified either, since the function is also indefinite.

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- "clarified morphology" or "abnormal morphology". It is not clear what measurable difference is classified as a clarified morphology and how it is clarified. Further, it is not clear what defines an "abnormal morphology" and what defines a "normal morphology." Was also addressed separately in individual bases of rejection to Claims 1, 2, 3,

- "differentiate" Claims 1, 4, 5, 6, 13. The use of the term "differentiate" in steps b, e, and f in Claim 1 is *confusing*. In other words the term is vague and indefinite because the meaning is not set forth in language which is clear and precise enough to distinguish between two standard definitions of the word, both recognized by cytologists and dictionaries.

- "differentiate" Claim 1, steps e and f. Further confusion is introduced in steps e and f with the recitation that differentiated cells are enumerated and examined, because technically the antecedent basis is incorrect since the cells of step b haven't been differentiated yet. "Confusion" in this instance refers to proper antecedent basis.

- Lack of correlation step. All claims. There is no correlation tieing examination back to the preamble (i.e. the goal) of the method.

- "Claims 2 and 14 do not specify when the blood sample is centrifuged and are *confusing*, because the language could encompass a blood sample that is first centrifuged and then placed in the tube. It's also not clear when the blood sample is combined with labeling agents and colorants". In other words, the order of the steps is not clearly and precisely set forth which renders the claimed invention vague and indefinite (i.e. confusing).

- "percentage of all labeled cells" Claim 2. There is no clear description of what percentage or percentage of what is identified.

- Claim 3. The order of the steps cannot be determined.

- "constituent components of blood" applies to claims 4, 5, and 6. The term is vague and indefinite because it is not clear what is encompassed by the term. Does this indicate separation of NaCl for water from other chemicals and molecules, for example. Clarification that the cellular components of the blood sample are separated is suggested.

- "insert that is operable" Claims 4, 5, and 6 are vague and indefinite in the recitation of an "insert that is operable", because while one of skill would be able to determine if an insert were generally cylindrical, the metes and bounds of an insert defined only in that it is operable to form a well-defined zone, which zone is not identified or characterized and is itself vague and indefinite as

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discussed above, cannot be determined. There are no identifiable characteristics of the claimed insert which allow one to determine if an insert meets the claim language.

-inconsistency between claims 4, 5, 6, 9 and 13 which renders them vague and indefinite because they do not clearly and precisely claim the invention. The claims recite the same method steps with different outcomes. However, there is no distinguishing description between these claims to account for the different outcomes from identical steps. See page 6, second full paragraph of the Office Action of 3/31/99.

“Axially elongated insert” Claims 7 , 9, 13. The term is vague and indefinite because the axis along which elongation occurs is not set forth.

“microscopical instrument” Claim 10. The metes and bounds cannot be determined.

“predetermined power” Claim 11. The metes and bounds cannot be determined.

“signal result” Claim 14. No characteristics of the “signal result” are supplied so the metes and bounds of the results encompassed cannot be determined.

Applicant has specifically responded to some of these rejections under 112 second paragraph, which response will be addressed below. Applicant has not responded to each and every grounds of rejection, however, given that clarification and separation of the rejection was requested, applicant’s response will be held fully responsive since each and every basis of rejection was not clear to applicant.

Applicant has indicated that the level of one of skill in the art has not been considered and indicates that if the level of one of skill in cytology is considered, the rejections are silly. This is not found to be persuasive. The specification does not disclose that the invention is directed only towards cytologists, but rather discloses that the invention is also directed to cancer biologists and to pathologists for use without extensive training (page 20 of the instant specification).

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Furthermore, while the claims are considered in light of the specification (and skill in the art), limitations from the specification are not read into the claims, which are given their broadest reasonable interpretation. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997).

Applicant argues that “constituent components” of blood would be clear to a skilled cytologist. This is not found to be persuasive for the reasons given above with regard to one of skill in the art. Further, blood is composed physically of cells and plasma. The cells of blood are composed of erythrocytes, polymorphonuclear lymphocytes, monocytes, and platelets. Polymorphonuclear lymphocytes may be further subdivided. The chemical composition of blood is far more complicated, including NaCl, water, urea, glucose, insulin, etc. Thus “constituent components” in its broadest sense may refer to basic physical components, individual cellular components, or chemical components, making the language indistinct and unclear.

Applicant contends that the rejection over “microscopical” instrument is disingenuous because it would be clear to one of skill in cytology and suggests the dictionary be consulted. This has been considered but is not found to be persuasive for the reasons given above with regard to one of skill in the art. Further, a dictionary definition of “microscopical” does not clarify the term. The definitions in Webster’s II New Riverside University Dictionary are 1) too small to be seen by the unaided eye but large enough to be studied under a microscope (i.e. an extremely tiny instrument), 2) exceptionally small (i.e. an extremely tiny instrument), 3) Marked by or done with extreme attention to detail, 4) of, relating to, or concerned with a microscope (this definition

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would indicate an instrument of some sort used with a microscope), or 5) suggesting or resembling a microscope in having the ability to observe very small objects (this one would indicate an instrument resembling a microscope but not a microscope). There is no definition of "microscopical instrument" provided in the specification in which to read the claim language in light of. Therefore, the term "microscopical instrument" is unclear. This rejection may be overcome by substituting the term -microscope.-

Applicant argues that "differentiated" is a common term in the English language and suggest a dictionary be consulted. This argument has been considered but is not found to be persuasive in light of the two common definitions of "differentiated", one being specific to cells. As stated in the previous Office Action, differentiated in terms of cells indicates a developmental state that results in diversity, which renders the claim language indistinct. This may be clarified by adding descriptive language. For example, the basis of rejection is not applied to claim 4 over "for differentiating cancer cells from hematologic progenitor cells" because descriptive language is included rendering the definition and claimed invention definite. If such language were inserted into claim 1, the rejection would be moot.

Summary of rejections under 112 first paragraph from the Office Action of 3/31/99:

-The invention is not described in such full, clear, concise and exact terms to enable any person skilled in the art to make and use the same. This basis of rejection was the reason the rejections under 112 second paragraph and first paragraph were combined, rather than repeat each of the reasons that the invention was not described in full, clear, concise and exact terms. For each of the issues summarized above, under 112 second, an issue of how one would be enabled to practice the invention if they cannot identify the proper scope of the invention, the steps, or the method compounds and compositions used. An additional issue was raised that one of skill (including

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cytologists) would not be enabled to practice identical methods with identical steps and obtain completely different results.

The additional 112 first paragraph issues introduced by the indefinite claim language were not addressed by applicant, however, the instant response will be held fully responsive since applicant was unclear how the basis of rejection under 112 second paragraph introduced issues under 112 first paragraph.

8. Claims 1-14 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Levine et al. (U.S. 5,834,217) and Rickman et al. (The Lancet. Vol. I, pages 68-71, 1989) in view of Nagy et al. (The J. of Exfoliative Cytology.-IDS) and Goldblatt et al (The J. of Exfoliative Cytology.-IDS).

The invention is drawn to methods of detecting nucleated epithelial cells, hematologic progenitor cells, or cancer cells in a whole blood sample by modifying the "QBC" technique to facilitate direct morphological observation within the centrifuge tube after densitometric centrifugation.

Levine et al. teach detection of nucleated cells by QBC technology. Levine et al. do not teach the individual examination of nucleated cells by microscopic morphology analysis nor do Levine et al. teach detection of epithelial cancer cells. Columns 7-10 and the abstract)

Rickman et al. teach that the QBC technique was well known in the prior art for separation and quantitation of leukocytes in blood. Rickman et al. teaches the tubes were known to be precoated with acridine orange (a colorant) which stained all nucleated cells. Further, it was

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known that individual cells within the well defined, stained layer were visible my microscopy. See Rickman et al. column 2 and 3. Rickman et al. modify the QBC technique to morphologically detect parasites. Thus, Rickman et al. teach that the modification of QBC technology to detect individual cells of interest for diagnosis was known in the prior art and was desirable for rapid mass screening (column 1 and the final paragraph of the article). Rickman et al. do not teach detection of epithelial cancer cells.

Both Nagy et al. and Goldblatt et al. teach that it was known that cancer cells were present and detectable in patient blood (see the abstracts and introductions).

It would have been *prima facie* obvious to one of ordinary skill in the art to modify the QBC technique to morphologically detect and quantitate individual nucleated, epithelial cancer cells with a reasonable expectation of success because QBC was known in the art to facilitate nucleated cell detection as taught by Levine et al. and to facilitate individual cell detection for diagnostic purposes as taught by Rickman et al. It was also known in the art that cancer cells (which are nucleated and epithelial) were present in the blood and diagnostic of cancer. One would have been motivated to detect individual cancer cells by QBC technology because Rickman et al. teach the advantages of rapid, mass screening using QBC.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564. The examiner can normally be reached on Monday through Friday from 830am to 630pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [paula.hutzell@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Yvonne Eyler
Yvonne Eyler
Patent Examiner

Yvonne Eyler, Ph.D.
Patent Examiner
June 18, 1999